accustomed to do that.

I am hopeful that perhaps including both of those, refractive to all currently accepted therapy and ineligible for cardiac transplantation may, in fact, help us to get to the severity of illness here, but I agree it is a major challenge.

DR. KONSTAM: Do you think that will do it or do you think you would want to be a little bit more rigorous at defining what that means?

DR. STEVENSON: It is exceedingly difficult to be more rigorous. I think judging from our experience with cardiac transplantation, we can certainly put in some of the constraints that we put in for transplantation, we can think about that.

If we look at the indications for entry into this trial, Class IV, EF under 25 percent, peak VO_2 less than 12, we all know plenty of patients like that who, in fact, would not have a 75 percent, two-year mortality. So, I think those may be helpful, but they are not adequate yet to get the severity.

DR. KONSTAM: I don't think we are going to wordsmith it now, but certainly there are guidelines for indication for transplant, and I

just leave it with the comment now that I think that if we are going to approve this, I think it will, in my mind, require some work to define, to make sure that patients who don't have, based on what we see here, an extremely limited life expectancy, don't get this device. Let me just say that, and say we are going to need to work on that.

The other side of it is a more societal question of putting it in people with comorbidities or advanced stage, and that can be more difficult to deal with.

Let me just ask, because it is sort of interesting, one of the entry criteria here was comorbidities. I mean that was a permissive entry criteria. You had to not be a candidate for transplant. That is one of the ways you could not be a candidate for transplant.

So, it certainly didn't exclude patients with, quote "comorbidities," but do you want to comment about what type of patients and what type of comorbidities you would not want to see receiving this device clinically?

DR. STEVENSON: At this point, I don't think I want to list them for the record. I think we all agree that there are a number of organ

system degrees of failure that we would not want to see. For instance, part of the success of the bridge to transplant program has been, in fact, that people have to be eligible for transplant to get into the bridge, and I think that some of those criteria, for instance, in this one, you couldn't have a creatinine over 3.5 to get into this trial.

I think that we will end up with some organ system function parameters, and I would, in fact, propose that hepatic function be a very important factor in here, but I don't want to actually suggest specifics at this point.

DR. KONSTAM: Who is going to do that, though, do you think that is something the panel is going to be able to do?

DR. STEVENSON: I think this is going to be a work in progress along with the patient manual, will be how indications should be specified, and I think it is impossible to divorce it from the people who, in fact, will be evaluating these patients, and I think that those should be people with expertise in evaluating end-stage heart failure. I don't think there is any way we can write something out here that we could give to someone in the community and have them make this

decision.

DR. KONSTAM: Okay. The other big concern I have is who is going to be putting these in. Let me just preface it by stating the obvious, that the results that you have here with--I guess I can't get away from it--a less than anticipated survival rate in the treatment group, nevertheless were achieved with extremely expert investigators, all of whom I guess had experience with this device as a bridge, I assume, so maybe I could just open that to your comments.

How do we assure ourselves that we are going to have this device used by clinicians who are capable of achieving at least this same degree of success with it?

DR. ROSE: I think the best way to assure that that is happening is with postmarketing surveillance, to know, we can all want that to happen, but I don't see how you can know that without doing it.

DR. KONSTAM: You wouldn't propose some kind of a certification process, a training program?

DR. ROSE: Absolutely. Aside from that, even for bridging, the use of these devices

requires mandatory training for centers, and even retraining for centers in the use of this device, and all of them now I would expect are going to participate in the ISHLT registry of devices, as well, which is the community's attempt to--

DR. KONSTAM: Not to take too much time on this, because I think this is a concern to me, and may be to other people on the panel, could you just expand a little bit, what might be the nature of a training program that people might have?

DR. ROSE: It is generally two to three days of going to an expert center where a device will be implanted in an animal typically, or two animals, as well as didactics. We teach several of these courses at Columbia, and there is a curriculum, a syllabus, indications, process of management to the patients, and the ability to participate in an animal implant with experts in device insertion is all part of the course.

Frankly, after the course, there is often a lot of dialogue, as well.

DR. KONSTAM: What about patient experience, what about actually assisting or participating in actual patient operations?

DR. ROSE: Why don't you speak to that for

the bridging.

MR. POIRIER: In the bridging program, we made the determination right upfront that no one would be allowed to use this device without going through a formal training session. The training session consists of two parts.

One is that we have a training center, and Columbia is one, where the physician and his team go to Columbia for two to three days, they implant the device in two different animals, they go through all of the issues in terms of patient management, patient care, patient selection, all of those things.

In addition to that, the company sends to the specific hospital that wants to use this, a team to train the nurses and the people who will take care of these patients, go through the operation of all of the systems with the engineering people on site, so that everyone is thoroughly trained.

There are manuals, operating manuals, patient manuals, a whole variety of different manuals that are used in this training. So, nobody will touch this device until we are convinced that they are adequately trained.

DR. KONSTAM: And in terms of other elements at the site, you know, in terms of the heart failure care or the ability to select patients, any thought about that? Should it be limited to certain sites or only certain surgeons?

MR. POIRIER: One of the advantages that we have is this is a close-knit community, everyone talks to each other. If there are any questions, people call each other and discuss it, and we have a whole network of people willing to do that.

If there are any issues on patient selection, there are many people who will discuss that. I think the physicians here will back that up.

DR. KONSTAM: Thanks.

DR. PINA: But I think you have to extend that a little bit differently, because up to now you are bridging classes, which I am familiar with, have been for transplant centers because that has been the approval, and now if a community hospital wants to put this device in, if it gets approval, they are going to be able to do it.

My worry goes even before the surgical expertise of the people that are putting it in, it is the people who are treating the heart failure,

and what we don't want to see in the heart failure community--and I am sure Lynne would echo this--is people being inappropriately treated for heart failure, and not being offered the therapy that sometimes is tough to do, but if you are persistent about it, you can get people on therapy, for example, beta blocker use.

It may be simpler to say, well, look, we now have this device approved. So, I think that Lynne's point about somebody not being a transplant candidate means that they must have gone through some process of being looked at as a transplant candidate, for whatever the reason, comorbidity, age or whatever.

That is my bigger concern even before, because I think you can train a good surgeon to do this and gather experience, but I want to go one step before this.

MR. POIRIER: We agree with that, we agree with Lynne. Don't think that there is going to be an avalanche of implants tomorrow. That won't happen.

DR. PINA: But that is something that has got into your training thinking beyond what you have done now.

MR. POIRIER: Yes, of course.

DR. PINA: I know your programs right now, and they are terrific.

MR. POIRIER: I mean as a company, we are concerned with that more than you are, because the results will be detrimental, and that will hurt us. So, obviously, we don't want that to happen. We will be very careful on how we let this out, and we will be very careful who gets it, and we will make sure that the people who are being evaluated are being evaluated properly.

We have a long track record of that. We have not been careless. I have been involved with this for 35 years.

DR. LASKEY: We are not impugning your integrity either, but the nature of the marketplace is also a wild animal at times. That is our concern, it is always our concern with these devices. It is not all up to you always.

DR. LONG: Clearly, responsible dissemination is utterly essential. We would agree with controlling that and making sure that there is excellence involved in this, especially until such time as it is appropriate to expand the volumes with adequate experience.

I would like to add one other comment about the patient populations that this is appropriate for. While we agree that this is a very high-risk patient population that should be receiving these devices, it would be unfortunate to constrain this field to serve up only patients that are very high-risk patients and patients who bring a burden, not because of the device, but because of their comorbidities to the process, so that we don't have the opportunity to improve the outcomes with these patients based on that particular feature.

DR. LASKEY: Nevertheless, we need to evaluate what we have in front of us. I understand you, and it would be wonderful if we had a distillation of what the gatekeepers went through, but we don't have that, and that is what we need, and I think that is what many of us are concerned about, is that that thought process has not been codified, it has not been translated into scalable covariates.

We have no idea who these patients are except for the fact that there was a 7 to 1 ratio between looking t them and putting them into this protocol, and that is not necessarily a

generalizable study result.

DR. COMEROTA: I would just echo Marvin's concern about indications, and I think inclusion criteria are one element that probably will be easier to identify than exclusion criteria, and I think it is fair to say that this panel would be very uncomfortable with defining that, and that is something that definitions need to be made and then brought to this panel.

I think many of those issues have been already enumerated, and some of them being societal, age, and are there going to be cutoffs, as well as other comorbidities.

I will just leave that as a comment.

DR. NISSEN: I must tell you that I am terribly disappointed in your inability to provide mean time to failure data. Let me tell you why. We have a device here that if I read Dr. Swain's review, failed in 20 of the 68 patients with an internal failure, not an external component, but an internal component, that is a 30 percent failure rate.

Now, for us to counsel patients about whether they ought to undertake such an operation without being able to say to them, look, if we put

this device in you, it has a mean time to failure of 12 months, and you didn't know that within an average of 12 months, you are likely to require replacement of the device, we have to know that.

The in-vitro testing data doesn't tell us that. Only the in-vivo data tells us that. So, I think that we must know how long we can expect this device to function for in order for patients to make an educated decision about whether they want to undergo an implant.

I am told the FDA is not interested in such data, I don't know if that is true or not true, but I am certainly interested in knowing how reliable is the device in a clinical in-vivo setting.

Can anybody give me any insight into that? I would certainly appreciate it.

DR. ROSE: I think to argue that there is no insight from this based on the survival data is just not correct. I think that patients, while they may be interested in failure rates and detailed failure rates, I think that most patients want to know even more how long can I expect to live.

That, unquestionably, I do believe we have

very firm data about, firm enough that I think it is reasonable for a physician to make a recommendation or to advise a patient as to whether or not it should be considered.

Without the approval of this body, those choices can't be made out in the public, and I think it is time based on this data set, that those choices be available to patients. The additional data, I think is desirable from the point of view of helping elucidate these issues, but from the point of there being critical to making a decision or not, as to whether or not this belongs out there for patients to benefit from is a separate question.

DR. ZUCKERMAN: Dr. Laskey, can I just provide a point of agency clarification on this reliability issue? I think the clinical question posed by Dr. Nissen is an extremely important one, and while the sponsor may have gotten the impression in the past that certain reliability calculation wasn't called for, et cetera, I don't think that that would be our current position.

In fact, I am going to ask Dr. Berman to better explain what we were trying to convey to the sponsor. It is also the reason why we do have

panel discussions like this one, just to better clarify what are the pertinent issues to, one, look at the device, and two, better capture information in our labeling.

DR. BERMAN: There may be a misapprehension of a misunderstanding. We would not accept reliability data from an animal study to demonstrate long-term reliability for a device. That is, typically, in the past, people have done eight cows for three months, and that does not demonstrate long-term device reliability in patients, it just doesn't, and we don't like that, and we tell people we won't accept that. We do want to see bench testing, there is no question.

We will certainly look at reliability data, data of rates of occurrence of different kinds of device malfunctions rate, time to occurrence of different types of malfunctions, and so on, as observed in a clinical trial. We will not accept that as the only data. We do want to see formalized bench testing.

Mr. Poirier is quite correct. Patient data is somewhat uncontrolled. You don't know under what conditions the device had a problem. There were at least one or two instances in the

REMATCH trial in which there was what appeared to be a device problem, but which we, in discussion with the sponsor, agreed was not, it was a patient problem. The device is not responsible for what the patient misuses.

So, to correct the misapprehension, yes, we want to know what happens, what is observed during the clinical trial, no, it is not by itself entirely sufficient, but it is very important, as in this case, to look at bench testing and how the clinical trial proves out that the bench testing was adequate or perhaps not completely adequate.

DR. NISSEN: One other question. I will ask the sponsor to comment on that. The other relates to the fact that the most common reason for not being eligible for transplantation is being over the age of 65. You suggested that there might have been some differences between how people did according to age.

So, I would be very interested in understanding whether there was a difference in the over-65 category. I know it was most of the patients. You suggested that the under-65 did particularly well. Is the converse also true, if you were over 65, did you tend to do quite poorly

with the device? Is that is the case, doesn't that speak somewhat to labeling?

DR. ROSE: We had three prespecified age strata in the survival analysis. One was less than 60, another was 60 to 69, and the other was above 69. In all of the age strata, there was a survival benefit of the LVAD arm. Only in the 60 to 69 group was that benefit statistically significant, but that was also the largest group, so I think it was reasonably powered to answer that question.

The younger age stratum that I described, that difference was not different compared to the others. I think as we accumulate more experience, that those kinds of data are going to be critical to deploying this kind of device.

DR. AZIZ: Just a suggestion and a question. Would it be reasonable to suggest that initially, at least for the next year or so, that the implantations only be done at centers that do transplantation?

DR. ROSE: Excuse me?

DR. AZIZ: That do heart transplantation rather than letting every community hospital be using this device.

DR. ROSE: I personally think that

dissemination to community hospitals at this point is not the way to go. I am open to argument. In particular instances, there may be a strong reason as to why a particular institution that doesn't do transplantation ought to have this available as an option, but in the early get-go, I think it is probably the wrong way to go.

DR. AZIZ: The other thing, I know that obviously, our discussion is related to this particular device, but I do believe that I think other devices have been used for long periods of time particularly in Europe. I don't have the numbers. I think the Quality of Life at least for those devices, the patients have done quite well.

DR. PINA: One small point. We learn from clinical trials whether the trials are positive, negative, or neutral, and I think as you look at the demographic data, which you apparently have not done right now, you may be able to come up with a risk profile for the patient who would be more likely (a) to have sepsis, the patient would be more likely to develop a CVA, looking at, say, vascular disease.

I would be particularly interested in you looking at the body mass index, which you can

probably calculate if you have the height and the weight--

DR. ROSE: We have that data.

DR. PINA: --and get some sense of muscle mass. I mean it's a very gross sense of muscle mass to look at the rate of--if you don't have albumin or pre-albumins--to look at the rate of complications based on the muscle mass or nutritional status.

DR. OSSORIO: I have two questions. One goes to the informed consent issue, and you had mentioned that these patients are so ill that it is not as though they are sitting around reading manuals or whatever.

Did you do anything particular in this trial to try to ensure that the informed consent was adequate? I am asking that question because I am trying to think about generalizing that, and thinking about perhaps unusual or special things that could be done in a non-research context, but that could help.

DR. ROSE: Oddly enough, I think one of the confirmatory issues around informed consent is the fact that the ratio of screened patients compared to enrolled patients was so high. I don't

think that we pulled any punches with regard to describing to patients what it is that was entailed here. Clearly, a large number of patients said with regard to a device, "I am not interested."

So, if anything, I think we bent over backwards and here the issue was clinical equipoise. We had the appropriate degree of equipoise in our posing these issues to patients.

Early on, I think there were questions around--I remember the first investigators' committee, there was still question as to whether or not this was an ethical randomization. I think we came to that conclusion particularly reassured when the DSMB looked at the first cut of data and just said to us, "Keep working."

That was enormously encouraging to us, so I think that we did have a reasonable degree of informed consent for the trial. I think the nature of informed consent though now, if the device is approved, is a different issue with a lot of other considerations, particularly the issue of concerns around overselling the device, and also I think it reasonable to have concerns around underselling it, too, that patients who could benefit from it, as you mentioned before, patients of color that could

benefit from it, that don't necessarily get it.

I think on both sides, we need to be particularly vigilant, and that is a challenge to us.

DR. OSSORIO: Another question, which I don't know if this is exactly a fair question, this is more for general information. Obviously, there are a lot of real societal concerns about investing tremendous amounts of resources extending to very, very end of life.

Did you and your company have any kind of an ethics discussion or particularly an ethics discussion about this that helped you to decide that it was a good thing to move forward with this kind of a trial as opposed to some other kind?

DR. ROSE: I don't work for Thoratec. The company I work for is Columbia University.

DR. OSSORIO: Right.

DR. ROSE: At my company, yes, we have considerable discussions around the ethics of doing this kind of dissemination. I think at the other end of the spectrum, though, can a society as successful and productive as ours, afford not to do this ethically, I think is as good a question as whether or not we shouldn't.

DR. LASKEY: Dr. DeWeese.

DR. DeWEESE: I have no additional comments. I would hope that your group would be able to provide a definition as has been asked for of just who would be accepted, but with your experience, and then it could be evaluated by the panel, if necessary, at a future date, and carried out.

DR. KLOCKE: I am sure you will do it. I guess I would encourage you to, if you could, one was saying codified, but you pointed I think correctly that the LDS in the Minnesota experience I understand with infection, which I have been focused on, appears to be different, and certainly anything you could do to codify that, to extend it to a larger group of patients if that really is a reasonable answer to the infection problem, it would be useful to, if the technology spreads, to be sure that other people don't go through the same learning curve that you have been forced to go through.

DR. LASKEY: Thank you. If there are no further questions, thank you, gentlemen, very much for a very persuasive and articulate presentation.

I am going to ask that the sponsors step

back from the table at this point, so that we can go through the questions again.

Panel Recommendations

DR. BERMAN: I am going to read into the record the questions we would like the panel to consider as they deliberate their decision for this PMA supplement.

1. The bench testing performed to assess device reliability did not account for all observed clinical conditions, in particular, higher than expected pressure in the pump chamber and higher than expected beat rates. Accordingly, the observed times to device failure and/or device malfunction seen in the clinical study are less than those predicted by the reliability model. As well, there is no reliable end-of-pump-life indicator. Please discuss the clinical implications of the observed reliability.

2. Are the device failure and malfunction rates and their time to occurrence appropriate for a device intended for use for destination therapy?

3. Given the Kaplan-Meier survival curves and the fact that 7 device patients and 3 control patients, as of February 02, had survived to 24 months, have enough patient data been reported to

demonstrate a clinically meaningful survival benefit?

4. The New York Heart Association, the Quality of Life, and the functional testing results are not consistent. From these data, can we determine that there is a clinically meaningful improvement in functional status?

5. This device demonstrated an increase in median survival time and showed an overall difference in survival. However, this benefit diminished at two years and was associated with serious adverse events and hospitalizations throughout the course of the study. Do the benefits of this device outweigh its risks?

6. One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize benefits and minimize adverse events.

6(a). Please discuss the appropriateness of the proposed indications for use for this device, which reads:

"The HeartMate VE LVAS is indicated for

use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from nonreversible left ventricular failure. The HeartMate VE LVAS is also indicated for use in patients with end-stage left ventricular failure who are ineligible for cardiac transplantation. The HeartMate VE LVAS is intended for use both inside and outside the hospital.

6(b). Does the labeling accurately inform patients of the risks of the device?

6(c). Does the labeling adequately inform patients of the expected duration of use for this device?

6(d). Are there any other issues of safety or effectiveness not adequately covered in the labeling?

7. Based on the clinical data provided in the panel pack, do you believe that additional clinical follow-up or postmarket studies are necessary to evaluate the long-term effects of this device? If so, how long should patients be followed, and what endpoints and adverse events should be measured?

DR. LASKEY: At this, Dr. Zuckerman, would you like some consensus opinion on each to these?

I can tick these off with the help of my colleagues, so, please, feel free to correct me if I am misquoting or misparaphrasing, any of you.

For Question No. 1, on device reliability, I think we have established the fact that we would like to see more data on device reliability, that what we have seen to date indicates that in the clinical arena, the reliability falls short of the predictions made from theoretical and in-vitro testing, and that we would like to see, as requested by two of the panelists, the distribution of the times to failure, not just the medians and the means, but all the data points.

Your colleagues, please feel free to contribute.

Is that helpful, Bram, am I touching on the high points here?

DR. ZUCKERMAN: Yes.

DR. LASKEY: With respect to Question No. 3--

DR. DOMANSKI: Could I just ask a question about that? That could also be after, that is the postmarket period also or could be if we choose to approve this?

DR. LASKEY: Yes, I am simply rehashing.

Mike, can you go to Question 3, data analysis?

DR. DOMANSKI: Shouldn't we talk about 2? I am not sure we really addressed 2.

DR. LASKEY: I am sorry.

Are the device failure and malfunction rates and their time to occurrence appropriate--but we needed to see more data up to this point, is that not correct? Dr. Nissen wanted to see means and medians to failure. A number of us would like to see the actual distribution of all the points, not just those two.

DR. KONSTAM: I agree, but I think we could discuss No. 2 based on best case of what we think we are seeing, that is, a device that lasts on the average about three years in vitro and appears to be somewhat shorter than that in the trial. This is asking the judgment question of whether--I mean that is how I interpret it--whether that is an appropriate level of reliability for destination advice.

DR. DOMANSKI: I guess the question I have is if you are going to do that, again, do you feel like there is not enough data in to consider this application, or can that be done by the FDA staff

after approval?

DR. COMEROTA: Wouldn't it be simpler to define destination? If the definition was one year of additional life versus four years of additional life, would the answer be clearer, and then the gray area gets in the 2 1/2 to 3?

The real crux of the matter is what is the destination.

DR. NISSEN: I guess what I was trying to get at here is that as I understand it, the patients lived an average of around 400 days, and during those 400 days of life, approximately 30 percent of the devices had an internal failure that could not be fixed without another operation.

That gives me some flavor for what the durability of the device is in a clinical setting, so I would be prepared to answer the question. I think I would answer it as no, that it is not reliable enough for destination therapy, it is reliable enough for a bridge to transplant, but in this application, my answer would be no.

DR. DOMANSKI: That is a fundamental question about whether or not this thing is going to be approved.

DR. LASKEY: We are overlapping with

voting now, so I think many of these issues will be more black and white as each member gives the reasons for yea or nay. So, that ultimately may be the answer to many of these questions.

DR. DOMANSKI: Yes, but I don't know that we have a consensus that you can give the FDA on No. 2 right now is the point.

DR. LASKEY: Then, let the record reflect that there is no consensus perhaps due to the wording or perhaps due to the issue itself.

I think Question No. 3, we are all uncomfortable looking at 7 versus 3, nevertheless, the P-values are statistically significant. My question to this question, is a clinically meaningful survival benefit, can it be viewed in isolation? It needs to be viewed in relationship to the associated complication rate. So, yes, we have demonstrated a survival benefit, but is it clinically meaningful if it confers a hazard of adverse events, as well?

Does the rest of the committee share that sentiment?

DR. WITTES: I don't think that the first clause and the second clause match, and I am having trouble with this because the problem is not only

that there is only 7 and 3 at 242 months. It's that there is a lot of censored data. So, it's not as if we had all 68 patients and we knew that the rate is 7 and 3. Then, we would have a good estimate of two-year survival rate.

The problem I think--I mean there are several problems--but one is that there is data in the pipeline that we don't know yet, and so I would like for you guys to reword that question to effect that.

DR. LASKEY: That would indicate that not enough patient data has been reported then.

DR. KONSTAM: Can we take a step back? I think there is a core question that probably it might be worthwhile to sort of have the panel reflect on, that seems to me to come through as you work through these.

It relates to reliability and it relates to this Question No. 3. That is the very essence of what REMATCH shows, and is the REMATCH result clinically significant, yes or not, and to me it all circles around whether if you have a statistically significant effect and apparently clinically very relevant effect at one year, but for the sake of argument, let's say that we are all

lost at two years, because we don't have very reliable data at two years, and there are concerns about the reliability of the device at two years.

If that is what we have, is that a clinically meaningful result, and before you get into the adverse effects, yes or no. I think, to me, from my point of view, I would love to hear the panel sort of try to reach a consensus about that.

DR. KLOCKE: I think Marvin stated it. I would have to vote no.

DR. DOMANSKI: Well, I don't agree with that. I think a year means different things to different people, and governments rise and fall in a year, our grandchildren are born, you know, it means different things to different people, and I think putting it on the market and letting people make their own decision is more to the point.

The fact is that the job of this panel isn't to make major societal decisions about resources are allocated. Our job here is limited to saying is it safe and effective, and, you know, I think the thing is safe and effective to extend life by one year.

DR. KONSTAM: Since I posed the question, I guess I will weigh in. I happen to agree with

Mike. I think that there are major societal questions that are hit upon by this application and I have to keep reminding myself that those questions are not before us, that the questions before us, and I think Mike sort of stated it, is this device safe and effective, and if you accept the core finding of the study--I mean one can challenge it, I mean I heard some challenges about whether there could be some bias introduced because some patients had the device and maybe were not DNR, and this sort of thing, that might be worth asking--but if one accepts the basic core finding that there is a highly significant prolongation of life even though it may well disappear at two years, I guess I cannot make a value judgment that that is not something we should offer to the patient.

DR. KLOCKE: I would understand and would agree with that, and could imagine circumstances in individual cases where someone has a daughter who is getting married in four months and wants--I mean I would certainly do that. On the other hand, I think, Marvin, at least for me, it depends on the meaning of the term "clinically significant," and I think that actually, I find it difficult, although

I understand the survival data, it seems to me that the data we have indicate that the window may well be closing, although you don't know that until the data are in, but I also have to judge that in terms of the full complement of the device, the prolongation of life at the expense of increased adverse events, which I think really is correct, and so it's a judgment business, which I personally have no problem that reasonable people would differ.

But I don't think in this circumstance, if I were dealing with one patient, I am the advocate for that patient, and I certainly would do everything I could, but I think "clinically significant," and I don't mean to consider it in a societal text or anything else, in the overall best medical judgment case, separate from society, separate from cost, there may be a clinically significant benefit, but I am not convinced at this point.

DR. NISSEN: I would like to weigh in on this one, too. Let me say that, first of all, I really do think this was a valiant effort on the part of everybody involved to try to make this work, but I don't think it worked very well, and I

don't think it was a clinically meaningful enhancement to survival.

I want to point out to the committee several things that we have heard today. Thirty percent of the patients that got the LVAD never made it out of the hospital, 27 percent had a serious neurological event, 31 percent had sepsis. Overall, 64 of the 68 patients had a serious adverse event.

So, if you said, well, we can extend your life by a year and we can avoid really large numbers of major morbidity and mortality, and we can improve your quality of life, then, I think it would be meaningful, but the Quality of Life data is very inconsistent as we have all talked about.

There is not really any solid evidence that that was the case, and I think the fact that so many people didn't get out of the hospital, so many devices failed during the course of the study, means that it was a good idea, but the device is not good enough to yet turn this thing loose on a population of people who undoubtedly are likely to be not as good at using it as the investigators in this trial.

So, I think that if we are going to let

the genie out of the bottle, let the genie out of the bottle for a device that really works well, and I don't think this device worked well.

DR. COMEROTA: I guess I need to make a comment. I don't necessarily agree with you, Steve, because if you take it on face value, these are exceedingly ill patients, there will be an operative mortality from a large operation, that we need to accept, and I think most of us probably do.

The bottom line is if we are focused at two years and beyond, I think there is discomfort, but the discomfort should be lessening with the updated data that we are presented, obviously, not quite statistically significant, but more convincing.

The bottom line is at one year, there is a significant increase in survival, and there is no device failure at one year, which we can accept. There must be improvement at the device level, and there will be. I thin the quality of life does parallel the findings in the improvement in the New York Heart Association functional class although we have to accept the possibility and the probability of bias, but they are parallel.

With that said, and a significance at one

year an device failure at one year, can we justify not approving it with the definition of the indication thrown in.

DR. LASKEY: I am not sure we can approve this device only for one year, though.

DR. DOMANSKI: Actually, it is not a matter of approving it for only one year. I mean one doesn't usually put into an approval the survival data of any of the devices we put out.

DR. DeWEESE: I think that we have good evidence that it does increase survival rate albeit it maybe only at one year at this time, but I think that there is going to be improvement in this device. I think this is something that we are going to have eventually, and I think this group that has presented this and the group that worked with them, should continue to do it, and I would hope we would support them to do this and make the advances that are necessary to make it a little better maybe.

DR. LASKEY: Maybe we could get just a little bit of help since we have really answered Question 4, as well, here, but Dr. Zuckerman, you might try and frame for us where the FDA is going with respect to changing definitions of survival

benefit.

This is clearly a very different relative risk reduction or reduced hazard ratio than we are used to thinking about, and the general rule of thumb has always has been the sicker the patient, the more dramatic you want to see the relative risk, or it is always the sickest who "benefit the most."

What is that the Agency has in mind with respect to a meaningful survival benefit if 25 percent is not enough or 33 percent?

DR. ZUCKERMAN: Can we go back to question 3, Dr. Berman.

When we look at our definition of "reasonable assurance of safety and effectiveness," we need to be able to demonstrate clinical utility. As indicated in the opening presentations, clinical utility for this type of device in this type of population hasn't been previously perhaps well defined.

Consequently, we are looking for some panel consensus, if possible, as to what a clinically meaningful survival benefit might be - is it what we see at one year, is it a difference in the median survivals for the two-patient

populations, even though the survival curves might come very close together at two years?

We don't have a priori a predefined definition, and we are looking for some help here. The fact that this is a gray area isn't surprising, but maybe you can poll panel members again to see if there is some more of a consensus.

DR. LASKEY: I will poll them once again. I would like to also suggest one more index of survival benefit, which is how much longer the patient is going to live, how many more days or months of life can one expect with this treatment, and I think that needs to sometimes be added to this clinically meaningful survival benefit in addition to a P-value. I think if we knew how many more days a patient had, that would answer the question that I think Dr. Rose posed to us, which was how much longer do I have.

DR. KONSTAM: Let me just give my reflection on this. I come at it the other way, which is that I see a dramatic statistical effect, a large number for risk reduction, a substantial augmentation in median survival, and a very low p-value.

So, the effect is pretty dramatic in my

mind. Again, to me, I compartmentalize the issue of adverse events, so I think Steve's points are very cogent and need to be addressed by the panel, but I think maybe separately.

To me, it is I think logically useful to first just go through the exercise of whether you think that there is a clinically meaningful effect on survival, yes or no, and to me I think there is a very dramatic effect on survival, and the question is do we feel that that is negated by the fact that we don't see it at two years.

This is to me the way I frame the question for myself, and I come away saying who am I to say that those findings are not important just because I don't see it in two years. You know, I am not the patient really being potentially presented with that choice.

I guess in terms of the survival effect, I am impressed with it, and I can't talk myself out of that.

DR. LASKEY: I am not sure we are any closer to a consensus. We keep going around and around. I must say as a clinician, I find it hard to divorce survival from the quality that goes along with that survival, and when there are so

many infections and strokes and re-ops.

It just can't be viewed in isolation. Statistically, it can, but clinically, we take care of the whole organism.

Janet.

DR. WITTES: I would look at it as at one year, I am coming in, trying to make a decision about whether to have this implant or not, then, the relevant data it seems to me, if I don't have it, then, my chance of being alive in a year is a quarter, and if I do have it, my chance of being alive in a year is a half, and that to me seems like a big difference.

I don't care about two years, I am talking about disease where my imminent death is--so, it seems to me that then what I personally would weigh, given those data, and I am comfortable with those data, the p-value for me tells me that those data are pretty robust, I am comfortable with those numbers.

So, then I would play into am I willing to take all these other risks to give me this benefit of mortality. My personal feeling, and I think as a panel member, that we shouldn't make that decision for other people, that I would say yes, it

demonstrates a clinically meaningful survival benefit.

People may not choose it, but I would say yes.

DR. DeWEESE: When I first read this, I thought that the persons who had had a number of adverse events, it would discourage them and make them feel they should not have done what they did, and then I find that an equal number of people who were controls and had the procedure said that they wanted to withdraw.

I would have thought there would have been a much higher withdrawal rate from those who had the procedure, had it, when they are looking back, had they been that person.

DR. NISSEN: One comment. I personally cannot separate survival from quality of life, and I will tell you why. Let's just take, for instance, for a moment, that you had a therapy that could prolong survival by one year, but all the patients were in a vegetative state during that period of time.

Would you call that a clinically meaningful survival advantage?

DR. WITTES: No.

DR. NISSEN: Just so we all are on the same page here, I think it is one thing to say there is a statistical effect on survival, and the other is to say there is a clinically meaningful effect, and I think the word "clinically meaningful" to me implies that there is some quality of life.

DR. DOMANSKI: What little data we have on Quality of Life, and, you know, I don't think much of the Quality of Life data in this trial, not because of any fault of the investigators, but because of just the nature of the study, but what little we have suggests, in fact, that although not absolutely consistently across things, it has improved.

Much of the chemotherapy we give is little more than chemical last rites in a setting where the patients know they are not going to get much benefit from it, so people do choose it.

Here, they have an opportunity to choose some benefit.

DR. KNAPKA: Again, talking from a patient that was in this condition, given like 30 days to live, and this sort of thing, I don't think a panel can make a decision whether one year or two years

is significant. There is just no way anybody can make this decision unless you have been there.

I think we probably need, if we feel very confident that this device will give the majority of people, and we realize that the tests we are looking at, these are real sick people, kind of a last resort.

I think this is one of the problems. There is a lot of these new devices and new chemicals that it is usually used on patients as a last resort, but I think we are arguing whether a year or two years is a significant amount of life, we will never come to that decision. It ha got to be a patient's decision, and I can't make that for anyone.

DR. OSSORIO: I just want to weigh in on the side that says clinically meaningful survival is something more than just statistically lengthened life. I want to weigh in on that side because I think that once you do, things begin to unravel here a bit, which is unfortunate.

DR. KONSTAM: I just want to clarify what I said earlier. I guess I was segmenting the issues, and to me I think it is worthwhile segmenting the issues. I took Question No 3 really

just to address the one-year versus two-year issue, and really that is what I spoke to.

I certainly concur with everybody else, but I do think it is worth getting past that and just looking at that issue in isolation if for no other reason for its logical value.

I certainly, however, would not stop there. I certainly concur that if we were extending life, but people were in a vegetative state, I would say now, okay, the numbers are okay, but forget it. So, I certainly agree with that.

So, the next question, I think the next logical question is okay, life is extended if you accept that, and is it meaningful. Well, I have trouble saying that we have not extended meaningful life here. If you look at six months, for example, in the LVAD group, you have 8 patients who are classified as New York Heart Association Class I, and 19 patients classified as Class II.

The corresponding numbers in the medical management group is zero and 2 patients. Now, I agree that this statistical analysis of the Quality of Life comparison is extremely problematic, but to me, comparing the Quality of Life in the two groups is much more important if you have most of the

patients alive.

If you have one limb that is 75 percent dead after one year, to me the question changes. The question becomes is the clear extension of life very problematic because very, very few of the patients are having meaningful life, and a best I can read into this, not having the patients in front of us, I see significant, clinically significant, in my mind, numbers of patients who are doing pretty well.

This really gets back to the comments that were made earlier, who are we to say it is not appropriate to offer that to patients. So, I agree it is a several-step process, and I wasn't up to that step yet, but I don't think you can look at this and say well, we are keeping everybody alive, but they are vegetative. There seem to be people who are doing pretty well here.

DR. LASKEY: I am sure Steve used that more for hyperbole than for reality, but it certainly makes the point, and I think certainly what we are all grappling with is we can easily deal with the easiest thing to do here is to interpret the p-value, as Janet has said, and say that there is a significant effect demonstrated

here.

However, we are clinicians, and I think that there is this nagging feeling that many of us can't get past when a survival benefit is associated with risks of bleeding or risks of sepsis or risks of stroke, and so on, and so forth, which is identical to the end of life chemotherapy issue, as well, and I am not sure there is a meaningful answer to that one either.

I am not sure that we can give you an answer to your question yes or no. I think you have heard the deliberations and the really assiduous thought process that we have put into this. This is a different category of patient, this is a different proposal here.

DR. WITTES: Several of you have said that I responded to the p-value, and I want to make it clear what I was responding to. I was responding to the difference in the magnitude of survival at one year, the 50 percent versus 25 percent, which I was interpreting.

You know, you may not agree with the interpretation as an important difference. What I said about the p-value was that the p-value made me believe that that difference was likely to be real,

but I was not reacting to, and I think it is important for you guys to know statisticians tend not to react to the p-value by itself, it is the magnitude of the difference.

DR. ZUCKERMAN: The fact that there isn't one clear-cut answer is okay. This is a difficult question that FDA has struggled with. Would it be fair to summarize, though, that panel members come to this question with different prior beliefs, and there is a range of answers as to whether or not a clinically meaningful difference has occurred at one year and throughout the course of the study?

DR. DOMANSKI: And you are going to get a quantitative estimate of that balance when they vote yes or no in terms of approval.

DR. ZUCKERMAN: Right. It just underlines the need therefore for a control in this study to better assess that risk-benefit profile.

DR. LASKEY: I think we really have beat up Question 4.

DR. ZUCKERMAN: Before going on to Question 5, though, can you just give us a quick summary for the record?

DR. LASKEY: I think I can summarize the panel's feeling as saying that, number one, it is

recognized and accepted among the heart failure community that measures in NYHA, 6-minute walks, et cetera, et cetera, don't always correlate. Number two, they are soft endpoints. Number three, unless they are blinded in their ascertainment, it is even more difficult, and the potential for bias is always there when you have unblinded observers assessing soft endpoints.

I think we would all like to read into this an improvement in functional status, but it is hard with those caveats.

DR. OSSORIO: I guess for me this is the crux right here. If people can't do better than this, I think we are in real trouble. I people should be expected to do better than this in terms of measuring something about whether or not there is a functional improvement or whether there is some kind of decent functioning going on in people's lives after they have had this intervention because what patients do care about is, you know, if what somebody cares about is I want to see my child's wedding or my grandchild's birth or whatever, if you can't recognize your child or your grandchild, it doesn't really matter, you know, that you are alive at that point.

There are ways of assessing these things. They may not be in the cardiology community, they may not be as widespread, but there are ways of assessing these things, and I think people ought to be expected to do it.

DR. DOMANSKI: I don't think that is an entirely fair analysis, though, because, you know, these people did go through the whole battery of things. There are certain things that are peculiar to an unblinded study where you put a device in.

DR. OSSORIO: I know.

DR. DOMANSKI: I think if you say that, then, you ought to offer some indication of how you think they could have done it better, because I think they did what they could, but it is the nature of the beast that makes it difficult to assess, so I don't buy into that statement.

DR. NISSEN: Mike, how about just having somebody who is not the operating surgeon ask the question about what your functional class is. I mean to me, you know, I can't think of a lower standard to apply than to have the person who actually did the operation asking the patient whether they feel better or not. That is about as bad a data as you can possibly generate.

DR. LASKEY: That perhaps will be recommendations for further study design.

DR. DeWEESE: Where did we have that evidence that the surgeon got that information? Was that in anything we received?

DR. NISSEN: That is what we are told, to ask the question, and that was the general gist of the answer.

DR. DOMANSKI: Since that is raised factually, is that really true, because actually, I didn't know that.

DR. OSSORIO: That question was asked.

DR. DOMANSKI: I took it at face value. Is that what they said? Okay.

Could I ask them to clarify that for us, please? Could I ask them to come back to the table and answer that question?

DR. LASKEY: The question being, so we are clear for the record, how was NYHA classification assessed and by whom.

DR. ROSE: We didn't specifically state that surgical patients should not be evaluated for NYHA class by the surgeon or the operating surgeon, and I can't say that there are data that don't reflect that. I think knowing how these clinics

and follow-up function, the overwhelming majority of patients were assessed by the cardiologists who were following them or the nurse clinicians who were following them, as well.

So, to think that this reflects, this improvement in NYHA class reflects some enormous blinding on the part of the surgeons doing this at some level is an insult I think to the participants in the study.

DR. LASKEY: The panel abjectly apologizes for any sense of insult. It wasn't meant to be an insult, but I think that the answer is that the investigators and/or their associates obtained this information. We certainly didn't mean to insult them.

DR. NISSEN: As opposed to an independent third party. I mean, look, I mean you asked if there could have been better methods, and the answer is that it would have been extremely easy to have a non-participating person do the assessment of functional classification, and that would have been the proper approach from a trial design point of view, and that was not what was done.

DR. DOMANSKI: I think there are some other things, though, that came in. It wasn't just

NYHA. NYHA class is tough, because don't forget, there is a big placebo effect. I mean if you bury one of these things in somebody's chest, they want to feel better.

So, I would be worried about that, as well, in terms of unblinding, but I think there were also, you know, they did the SF-36, you know, they did a bunch of things and stuff.

DR. KONSTAM: I completely agree with the points that were made, but I still keep coming back to the fact that the control group had so many dead people in it, so the issue really changes. I mean if you had 90 percent survival in both groups, you would really want to know which group is doing better.

When three-quarters of the control group is dead by a year, I think the question changes. The question becomes one, which is much more difficult to answer, which is how is the treatment group doing, and do we have a sense that they are all vegetative, do we have a sense that they are all hospitalized, or do we have a sense that at least a sizable number of them are actually doing okay, and looked at it that way, you know, I think the data are adequate for me to say, you know,

there are sizable numbers of patients that at least at six months and a year are doing okay.

DR. LASKEY: And that you can't be doing well if you are dead.

DR. KONSTAM: You can't be doing well if you are dead.

DR. LASKEY: No. 5. I think we have been grappling with the denominator here, that is, the benefit as it relates to Question No. 3 and the data analysis and the magnitude of the clinically meaningful survival benefit, that being the denominator of the risk-benefit ratio.

Do we need more discussion about the presence of risk or do we need to focus in on the magnitude of this risk and how it relates to that ratio?

We all agree that there is risk with this device. Where is this ratio, is it closer to zero or closer to 1, I guess is what you need to know.

DR. BERMAN: I think the panel has discussed this question along with the others.

DR. LASKEY: Okay.

DR. PINA: Let me bring up one point that hasn't been brought up, and it is part of the protocol, and that is the issue of cost, which has

not even entered into any of the data that we have, but the expense even on a surviving family member may be some of the risks that have to be assumed other than just the physical risk.

So, I think that is something we need to keep in the back of our mind even though that is not part of the data that we have.

DR. ZUCKERMAN: Again, Dr. Laskey, for Question No. 5, the question is do the benefits of this device outweigh its risks. Is there any consensus at this point from panel members?

DR. LASKEY: What I am hearing at this point is I don't think there is consensus, you may see consensus or lack thereof with voting in several minutes, but I think right now we have aired the concerns about both the numerator and the denominator, and their relative weight will be reflected in how people vote.

DR. KLOCKE: I would answer that as possibly, but not clear to me at this point.

DR. LASKEY: Labeling. I think it is fair to say we have had an extensive discussion about the nature of this patient population. What is missing is how the investigators got there and how that translates into more detailed information in

the IFU, I am not convinced that we have heard that.

DR. BERMAN: Is it fair to say that the panel thinks there needs to be more details or more specific indications?

DR. OSSORIO: Yes.

DR. PINA: Yes. I think in the patient booklet, where there is a whole series of warnings, and I understand what Eric said, that a lot of these patients are not exactly going to be reading this great detail, but the relatives will be, and the spouses very often do, that all the complications that have been found in the study need to be enumerated, so that the patient is well informed and the spouse is well informed about all the risks, and that is not in there.

DR. COMEROTA: Which includes those who are indicated for the procedure, as well as those who are not indicated for the procedure.

DR. KONSTAM: Can I just make sure that the point is made and see if other people agree, that based on what we see in the REMATCH study, this device should only be indicated for people who are severely ill and with an extremely limited life

expectancy.

Now, there were some comments on that made both sides, but I think based on what we see in the survival data at two years, and those of us who think it is acceptable or not acceptable, nevertheless, most of the patients in the device group are dead at two years, and therefore, I cannot imagine doing anything other than approving this device for patients with an extremely limited life expectancy without this device.

Now, how you get there is for further discussion, but I think that would be the sense that I would want to inject into it.

DR. DeWEESE: I would agree.

DR. LASKEY: Does the labeling accurately inform patients of the risks, well, there were certainly conspicuous warnings and cautions, and so forth, which relate to I think mechanical malfunction. I am not sure what the data are there on the risks of infection and bleeding, and so forth.

DR. PINA: It's not in there.

DR. OSSORIO: Along with accurately informing about risk, if there are things that patients can do to minimize those risks or their

family members and people who are helping them if they happen to go home, those things ought to be in there, too.

DR. KONSTAM: I would say that this cuts to the heart. We talked earlier about patient choice. If we wind up approving this, I think some of us are going to say we are doing it because we think there should be an option for the patient, but if it's an option for the patient, here, really more than any other application for anything I have ever seen, we really have to take pains to inform the patient of what he or she is getting himself into and what kind of adverse events have been observed over the two years of this study.

You know, here is one where I don't mind scaring the patient, to tell you the truth, because of the degree of uncertainty that we have and what we have seen in this trial. I think a good deal needs to be done with this document to make sure patients adequately get a sense of that.

DR. PINA: I think also, in all fairness to the sponsor, they probably haven't seen these kinds of complications because this is a sicker group than I have ever seen LVADs in, because most of these patients, we would not transplant, and

therefore, we would have not have VADed.

So, I think in all fairness, this is probably their first experience with this very, very sick cohort where these complications were arising. This isn't the usual.

MR. MORTON: One point of clarification I would make is I have heard the panel refer to letting the genie out of the bottle, and that is a connotation of something that is out of control, and labeling is very much a way that release of this device could be controlled.

I know that on devices of this type, the FDA and the sponsor work together to very clearly define what the training program is going to be and what the release program is going to be, so I would like us to move away from the genie out of the bottle image.

DR. LASKEY: Fair enough.

Does the labeling inform patients of the expected duration of use?

DR. WITTES: It needs more.

DR. LASKEY: Very good, Janet. Needs more.

DR. KONSTAM: I would be fairly draconian about this. I think that the panel has some

serious, at this point, lack of information and uncertainty about the duration of this device, and I think that somehow again, I think the patient needs to be informed of that.

I think the comments that's in the proposed wording is simply that sometime in your life, you might expect to have to have this replaced. Well, I mean that sort of begs a lot of the issues that we have raised like there is no indicator of end of life, number one, so what is the implication of that.

Secondly, how many patients do we have now experience with, who have had successful reimplants and alive? I think there is one such patient who has had reimplant and are alive. Maybe there is more than one. Two? Okay, two. That is a very, very, very, very small experience, and to have that reflected by a comment that says at some point you might have to have this changed really strikes me as pushing it.

So, that wording really has to be rethought, and I think based on what we see right now, it should be made very blunt that we don't fully know the expected life expectancy of this, and somehow these points needs to be brought out.

DR. LASKEY: No. 7, PMA, postmarketing. I think we all would agree yes. There is a need for additional clinical follow-up specifically, and there is certainly a need for more appropriate risk stratification for who will benefit or who won't.

DR. ZUCKERMAN: Can you comment on what the major questions would be to answer in any sort of postmarket experience?

DR. PINA: Let me start out by again expressing my concerns about the internal device malfunction and the lack of knowing when it is going to malfunction, and I think the company has experience in the bridging group with perhaps the same problems, and all these other variations have been made, like the SNAP, the different wiring system, and I think we need a body of data on internal pump malfunction with all the advances and all the improvements that the company has made. I don't think we have that, and I certainly haven't seen it.

DR. DOMANSKI: One thing you will gain with your postmarket surveillance is you will gain a sense of the time course of the different types of complications - patient complications, device complications, and so forth, with this device, and

then other ones that come along.

So, actually, I think the postmarket surveillance in this case could be quite useful, particularly as the device evolves or devices like it evolve.

DR. KONSTAM: Can I add one other thing, I guess to come back to, I had raised earlier, is the question of anticoagulation. I just would like to see going forward some consideration of potential anticoagulation regimens.

I don't know what that would be right now, but we are seeing, to me, a higher than expected number of what I consider thromboembolic events, and I don't understand all the bleeds, but I think that that should be addressed with some postmarketing research.

DR. LASKEY: Certainly, first of all, with collection of information to get a better idea of the rate because it is entirely possible the rate may be higher in real life than in the trial settings. So, additional ascertainment of endpoints. Okay.

Open Public Hearing

DR. LASKEY: I would like for the last time today to open the forum for public hearing.

Is there anyone in the audience who wishes to address the panel on this topic?

[No response.]

DR. LASKEY: If not, then, I will close the public hearing and request that the sponsor come forward and give us your final sentiments.

Sponsor Comments

MR. MIDDLEBROOK: Certainly, all aspects of the study have been discussed thoroughly here today, and we just want to thank all the panelists for their insight and their analysis.

As a company, we are committed to, as Vic said, continuously improve this product, and if we look at our experiences from the bridge to transplant, generally speaking, our results have improved from the time when we did the clinical trial. We would hope that that improvement would be seen here as we look at this nascent therapy.

Again, I would like to thank the panelists, the FDA, and certainly all of our presenters.

Thank you.

DR. LASKEY: Thank you.

I would like to ask Dr. Ewing to read the voting options.

Panel Voting

DR. EWING: The panel recommendation options for premarket approval applications are the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency.

The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as, "Reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions of intended use outweigh any probable risk."

Effectiveness is defined as, "Reasonable assurance that in a significant portion of the population, the use of the device for its intended uses and conditions of use, when labeled, will provide clinically significant results."

Your recommendation options for the vote

are as follows:

Approval if there are no conditions attached. Approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the panel.

The third option is not approvable. The panel may recommend that the PMA is not approvable if: the data do not provide a reasonable assurance that the device is safe, or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting, the Chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. OSSORIO: May I ask for a point of clarification?

DR. LASKEY: Yes.

DR. OSSORIO: That very last thing that you just said, under the proposed labeling. Now, we have all made quite a number of suggestions

about what we think ought to go on the labeling, so when we are voting, are we voting assuming that those suggestions would be incorporated, or are we voting based on what we have right now in this packet?

DR. EWING: If the panel feels that to be approvable, then, the changes in labeling would be necessary, then, that could be approvable with conditions.

DR. LASKEY: It is your prerogative, Dr. Konstam, to make a motion.

DR. KONSTAM: I move approvable with conditions.

DR. LASKEY: And they would be?

DR. KONSTAM: I have a bunch.

DR. LASKEY: First, we need a second.

[Second.]

DR. LASKEY: You have a second, so you might want to delineate the conditions.

DR. KONSTAM: I have a bunch of conditions, and I think they have all been touched upon. One is additional analysis of existing data. The two that occur to me are revisiting the whole question of reliability, bringing data up to date, and getting a clear indication of reliability at

two years.

Secondly, that analysis that Mike Domanski had suggested of time to death or stroke be looked at to be certain that it is at least consistent with the observation with regard to survival. So, existing data would be one.

Secondly, the indications for the device be much more extensively delineated particularly to denote a population with a very limited life expectancy without the device implanted.

Third, that there be fairly rigorous criteria for implantation from the perspective of both the surgeon and the facility at which it would be done to be certain that both patient selection and expertise in the procedure and in patient follow-up meets a high level of acceptability.

Fourth, that there be a significant amount of postmarketing work be done surveying patients in whom these are implanted as least out to two years with analysis of reliability and analysis of all of the other adverse effects that we saw here and their rates.

I had mentioned earlier I would include in that some kind of consideration of the need for anticoagulation.

Finally, that there a lot of work go into a detailed set of information for the patients that really, as best as can be accomplished, delineates for the patient what the tradeoff is that he or she is getting himself into with this.

DR. LASKEY: There are five conditions then, and we need to vote on each one separately. Can we have some discussion amongst the panel members about Dr. Konstam's first condition, which is the requirement for more data analysis from the current data set?

DR. NISSEN: Could I understand this, does that mean that it would not be approvable until the data is analyzed, is that what you are saying? I am not sure I know what you mean by that.

DR. KONSTAM: Well, I guess I would want to ask the Agency what the options are in that regard.

DR. ZUCKERMAN: You are making a recommendation whereby potentially the device is approvable if these conditions are met.

DR. DOMANSKI: But I thought that what you meant was that these analyses would take place over time. You know, if you don't think it's approvable until they meet it, that is different than saying

we are going to do postmarket surveillance after.

DR. KONSTAM: Let's take the one that you suggested, the analysis of time to death or stroke. You made a compelling argument for that.

DR. DOMANSKI: I think that is fine. I think that is an easy one for them to come in with, and I think the numbers of events are such that that is not going to be a land mine in the field for them, but that is something they can go over with FDA staff, so that is fine. They are not going to have a problem with that.

I will just finish discussing the question. I would suggest that they not be forced to go out and gather new data.

DR. KONSTAM: What I meant with regard to the reliability is more detailed analysis of existing data.

DR. EWING: If you do not believe that there is sufficient information currently here, then, it would make more sense to vote not approvable, if you are talking about you need the results of current analysis.

DR. KONSTAM: At least what I had intended was pretty much along the lines that Mike was suggesting. I do think that the first part of that

is the analysis of death or stroke. I would like the Agency to hear my sense that I am assuming, Mike is assuming that that analysis will not radically change the overall survival analysis, and if it did, if it looked like all of a sudden it was substantively different--and I don't know how to advise you better than that--then, I would reconsider my approval. I don't know how to convey that.

DR. DOMANSKI: I have a suggestion. I will tell you what I really think. I think the number of events is not going to be sufficient to make much difference, and I would leave that out, delete that from your motion, and let the FDA just look over the entire application, because this is a recommendation, and not put this in as some kind of a firewall. I can't imagine it would, and the FDA is going to look at this thing. I just don't want to see them disapproval over something like that.

DR. KONSTAM: I think we are saying the same thing. I think the Agency has the prerogative of looking at the data and say you know what, I mean they can do whatever they want with it. They don't have to accept our final vote, so I guess we are saying the same thing.

DR. DOMANSKI: One way of doing this would be to structure the recommendations on things that need substantive change. I mean the FDA is going to go over this whole application again, but there really are some substantive things that they have to do.

The panel wants different labeling, so they are recommending that.

DR. LASKEY: He has put five recommendations, five conditions on the table for his recommendation. We need to either take them apart or just whittle that down to one or two. Can we try and do that, so we get a coherent, articulate vote?

DR. KONSTAM: Let me then clarify. I guess I would still stick to my first one, but I am not basing approvability--

DR. LASKEY: The first one being--just so we are all on the same page here--is additional data analysis as pertain to device reliability and?

DR. KONSTAM: And analysis of time to death or stroke.

DR. LASKEY: Time to death or stroke in the current data set.

DR. COMEROTA: And the purpose of that is

not for device approval, but better judgment on the basis of physicians and patients in the future upon whether their decision should be to move ahead with their own decisionmking or not, more informed consent on the patient's part.

DR. LASKEY: Yes, it is to be added to the labeling, is that correct? Okay.

Enough discussion on that condition? Shall we vote? Voting on these two conditions to Dr. Konstam's motion for approval, the first condition being additional data on device reliability and additional data on time to death or stroke.

DR. WITTES: Analysis.

DR. LASKEY: Analysis, yes, of the current data set.

DR. OSSORIO: Can I ask for a point of clarification? Could we vote, say yes on the various amendments, and at the end, still vote no on the motion?

DR. LASKEY: Yes.

DR. EWING: For the first condition, we need to go around the room, start with Dr. Wittes, please.

DR. WITTES: I am going to vote no. I

think it should be a recommendation. I don't see it as a condition.

DR. DOMANSKI: So, this isn't framed as a recommendation, is that right?

DR. EWING: This is the first condition of approval.

DR. DOMANSKI: I will vote yes to that, fine, do the analysis.

DR. KONSTAM: I vote yes.

DR. COMEROTA: I vote yes.

DR. NISSEN: Either we need more data or we don't need more data, and since I would like to see more data, I am not sure whether voting yes is going to let us look at more data before we make a decision, so I am going to abstain. I mean either we need these data in order to make a decision or we don't. I think I need these data in order to make a decision. Lacking those data, I don't think the amendment helps me.

DR. AZIZ: Yes for Dr. Aziz.

DR. PINA: Yes.

DR. OSSORIO: Yes.

DR. DeWEESE: Yes.

DR. KLOCKE: Yes.

DR. EWING: Thank you. I will tabulate

that that is 8 yes, 1 no, 1 abstain. The condition carries.

DR. LASKEY: Are you happy with the distillation of the conditions?

DR. ZUCKERMAN: Yes.

DR. LASKEY: Any discussion on Dr. Konstam's recommendation for additional clarification or new indications for use? Do we need to go through that?

DR. PINA: No, I think we have discussed that pretty well, and it may merit some other meeting at some point to sit down and really go through, and the Agency can do this, to go through the patient population that, in fact, would be eligible for this.

DR. EWING: Okay. We can take a vote although Dr. Domanski has stepped out. We will come back to him.

Dr. Wittes.

DR. WITTES: Yes.

DR. KONSTAM: Yes.

DR. COMEROTA: Yes.

DR. NISSEN: Yes.

DR. AZIZ: Yes.

DR. PINA: Yes.

DR. OSSORIO: Yes.

DR. DeWEESE: Yes.

DR. KLOCKE: Yes.

DR. EWING: That is almost unanimous for No. 3, the conditions for clarification of indications of use, clarification of the patient population indicated and excluded.

The next was the postmarket study.

DR. KONSTAM: No, the next is criteria for use both in terms of the operator and the site be clarified to be certain of high quality in patient selection and in performance.

DR. LASKEY: And training and experience.

DR. KONSTAM: But it is a little bit more than training. Training and--

DR. PINA: Setting standards?

DR. KONSTAM: Setting standards for both the operator and the site.

DR. LASKEY: So, what you would like to see the Agency receive is a document outlining the criteria for credentialing, if you will.

DR. KONSTAM: Right, and the spirit is that it be fairly rigorous.

DR. PINA: And could I add that it is not just limited to surgeons, but also to cardiologists

taking care of this patient population.

DR. KLOCKE: And could I ask that it include the group's best recommendations at that point in terms of infection control in relationship to the issues that I have been talking about?

DR. KONSTAM: That is fine with me.

DR. AZIZ: Do you want to restrict it to transplant centers?

DR. KONSTAM: Well, I held back from saying that. Maybe it is worth some additional discussion on the part of the panel about how far we want to go and what we mean. I mean I would be happy with limiting it to transplant center if other people on the panel would.

DR. LASKEY: I think in deference to Mr. Morton who raised the point that we really should not concern ourselves with how this device is used or abused, we just need to go forward in good faith and outline criteria for training and experience of these centers and individuals, realizing it is a system as much as people.

DR. KONSTAM: I thought he was saying that it is these very processes of labeling and training that give us a comfort level that we are not "letting the genie out of the bottle" by doing

these things.

MR. MORTON: Thank you. That is true. Again, from my experience on a device of this type, it is a collaborative process with the Agency of exactly what the training program is going to be and exactly how the release will happen.

DR. NISSEN: I am glad you all have faith that nobody ever uses devices off label.

DR. ZUCKERMAN: I think the issues from the Agency perspective are, one, two, consider Dr. Konstam's motion that the training program be rigorous and looked at by FDA. The second part is that potentially, as a postmarket requirement, one can look at how new sites are brought up to speed, et cetera, but there are two parts, and Dr. Konstam is first just asking about the review of a training program.

DR. KONSTAM: Did you want more specification to that or do you feel like leaving it as clear as we have is sufficient?

DR. ZUCKERMAN: Why don't you try restating it, so that then we can have a vote.

DR. KONSTAM: I think the spirit of what I would like to convey is that this device be implanted in centers and by individuals who are

highly trained and specialized in the management of patients with end-stage heart failure both from the perspective of patient selection and surgical procedure, and perioperative management and long-term management. I guess that is really what I meant now.

DR. ZUCKERMAN: Are you asking FDA to review the company's training program as a condition of approval?

DR. KONSTAM: Yes.

DR. LASKEY: That is fairly straightforward. Do you want to just do a hand vote?

DR. EWING: Sure.

DR. LASKEY: All in favor of this condition?

[Show of hands.]

DR. EWING: I believe that is unanimous. Is that correct? Okay.

DR. LASKEY: As I recall, the last condition was--

DR. KONSTAM: There were two more.

DR. LASKEY: Sorry.

DR. KONSTAM: Next was the postmarketing, and then the final one was information for

patients.

DR. LASKEY: Let's take the first. Maybe I misunderstood. The information requested from postmarketing surveillance would be?

DR. KONSTAM: Well, we talked about it before, I think developing a sizable body of experience at least out to two years, tracking patient survival, tracking complications, tracking device reliability and durability. There may be others people want to add to that.

DR. COMEROTA: Marv, would you be comfortable in extending that to death since a large percentage of those who have lived two years, died shortly thereafter? I would like to see it extended out to death.

DR. KONSTAM: Sure, so indefinitely.

DR. COMEROTA: Yes.

DR. KONSTAM: To death, yes.

DR. COMEROTA: Well, death is rather definite.

DR. KONSTAM: Definitely.

DR. LASKEY: Marv, given the limited capability of the Agency to do these kinds of surveillance, what would you recommend that they focus on, that they require?

DR. KONSTAM: You mean in terms of duration of follow-up or in terms of what they are looking at?

DR. LASKEY: More what they are looking at.

DR. KONSTAM: I think the things that I listed shouldn't be too onerous. I mean patient survival, device survival, and major complications, at least the major complications as were demonstrated in this study.

DR. PINA: Implantation rate.

DR. KONSTAM: That is device survival.

DR. LASKEY: This is all in the form of a registry, or are you recommending the conduct of an additional trial, if you will?

DR. KONSTAM: Well, I wasn't recommending a randomized trial.

DR. DeWEESE: Can't we just ask for what they have done in the first two years? That is what we want them to do, we want to get the same information we had before.

DR. WITTES: We are asking for less, I think, than what they did in the first two years. It seems to me we are talking about a registry.

DR. ZUCKERMAN: At this point, Dr.

Konstam, perhaps you can help us with what major questions you would like to see answered in a new cohort experience, and then the Agency and sponsor can work together on what type of trial design might be optimal, but if we can first define the questions.

DR. KONSTAM: I would like to know the life expectancy after implantation. I would like to know reliability and longevity of the device. I would like to know the frequency of the major complications that were identified in this trial, and I guess I would add to it and ask for some discussion or comments, you know, some indication of patient function, some indication that patients are doing well, and I don't know if people want to discuss what that should look like, but something more than that they are just alive.

DR. AZIZ: Also, I think it would be important when a patient dies, that the device be examined by one center specifically, so any valve problems or any motor problems could be documented, because I think just because the patient dies, there may be different reasons, maybe sepsis. I think the devices must be examined and explanted.

DR. PINA: I would like to echo the

functional capacity assessment because there are a lot of data on functional capacity and bridge to transplant, and that is well published and well known. So, I would like to see how this compares.

DR. KONSTAM: I also again would like to see something explored with regard to anticoagulation. I guess I don't want to make that more definitive right now except to say that I would like some sort of study proposed in the next six months, say, to explore--

DR. LASKEY: You need a handle on the rates.

DR. KONSTAM: My feeling would be that we already have from the data set in front of us, evidence that there is an excessive rate of thromboembolic events, more than anticipated. That is my interpretation of the data. Maybe there will be some differences of opinion on that.

DR. COMEROTA: I thought they were less for a totally implantable prosthetic without anticoagulation.

DR. KONSTAM: Less than what?

DR. COMEROTA: Less than anticipated.

DR. DOMANSKI: I have a sort of process problem with that, and the process problem is this.

We are approving this. All of the data that have come in here, have come in without the anticoagulation.

Now, we are approving the device, and you are trying to mandate a study that basically send them off label to do some anticoagulation. I don't think we can do that. I mean I think it is a good research study to do, but I think somebody ought to apply to NIH. I don't think we should be asking the sponsor to try to do something that is off label.

DR. COMEROTA: It is part of the condition, what you are saying, it would be appropriate to document that platelet inhibitors, what anticoagulants the patients are on, and monitor the outcome as a registry.

DR. KONSTAM: That's fine. If there is no objection, I would amend it to say that special attention should be placed in the postmarketing survey to examine rates of thromboembolic events with an eye toward considering subsequent investigation based on what events rate is seen.

DR. LASKEY: I think that is fine in concept, but there is not going to be a DSMB, there is not going to be adjudication committee. This

may be a tough one. I agree with you it is important, but it could be an under- or an over-estimate unless somehow it is ascertained appropriately or accurately.

DR. KONSTAM: Can't the FDA--

DR. LASKEY: You need to make that recommendation clearly in this condition.

DR. ZUCKERMAN: Yes, in the condition of approval, you can also ask that an independent CEC, similar to the original randomized study, continue to look at events to better clarify what are actual rates.

DR. KONSTAM: I could live with that.

DR. LASKEY: The registry's requirements are getting longer.

DR. KONSTAM: That's fine. I don't have any objection. That doesn't bother me.

DR. LASKEY: Are we all clear on what we are voting on then for Condition No. 4, which is the recommendation to the Agency in terms of establishing a registry for purposes of postmarketing surveillance to assess rates of--

DR. KONSTAM: --survival, device failure, and major adverse events including thromboembolic events.

DR. LASKEY: All in favor?

[Show of hands.]

DR. EWING: So, everyone except for Dr. Wittes?

DR. WITTES: I am going to abstain.

DR. LASKEY: And your last condition was the instructions for the patient information pack?

DR. KONSTAM: Yes, that the patient information package really--

DR. LASKEY: Serious buffing up.

DR. KONSTAM: Yes, make clear the risks and what the patient is getting into.

DR. LASKEY: So, rates of adverse events and certainly perhaps the addition of some help rewriting it. It is highly technical, I will agree.

Can we vote on that?

DR. AZIZ: The device once it's explanted, should be sent to a center.

DR. LASKEY: I like that idea. I don't know how you can mandate-- you mean explanted--

DR. AZIZ: When the patients die.

DR. LASKEY: Well, when they die, doesn't that require consent or permission? I don't know if you can mandate that.

DR. DOMANSKI: I wonder if they are not getting those devices back anyway. Maybe we could ask them that, because that may be an easy one actually. Are you getting them back?

MR. MIDDLEBROOK: Yes, we do like to get the devices back, and we do take them apart and disassemble them, and we do an analysis on them. We collect that data and analyze it periodically.

DR. LASKEY: Can you require that, though?

MR. MIDDLEBROOK: I don't think it can be required because they refuse to return it, and we can't mandate that.

DR. AZIZ: That is really the only way, if these devices are going to be in for a long time.

DR. LASKEY: I would agree. I can see a family just refusing permission.

DR. AZIZ: That is a different issue, but I think all efforts should be made, because that is the only way, if these devices are in for four years or three years, we are going to learn something.

DR. LASKEY: I would agree. Should that be in the patient package then?

DR. DOMANSKI: I think it is great to inform. I was actually part of a trial where we

did that once. I would stop short of informing them about what should go on at their autopsy. That probably is unreasonable.

DR. LASKEY: So, voting on the condition for the modification of the patient information package as currently written.

DR. KONSTAM: Let me just add to that, that based on what we see right now, there should be some indication of the limited present life expectancy of this device.

DR. LASKEY: Full disclosure.

All in favor?

[Show of hands.]

DR. EWING: That is unanimous for the last condition presented so far.

DR. LASKEY: That's the end of Dr. Konstam's list.

I shudder to ask this question, but are there any other conditions?

[Laughter.]

DR. LASKEY: No. Well done.

DR. EWING: I would like for the panel members to go around now and just state their vote for approvable with conditions. We might as well start with Dr. Wittes again.

DR. WITTES: Yes.

DR. DOMANSKI: Yes.

DR. KONSTAM: Yes.

DR. COMEROTA: Yes.

DR. NISSEN: Do you want yes or no, or do you want explanations?

DR. EWING: I want a yes or no first.

DR. NISSEN: No.

DR. AZIZ: Yes.

DR. PINA: Yes.

DR. OSSORIO: No.

DR. DeWEESE: Yes.

DR. KLOCKE: Yes.

DR. EWING: So, that is 8 yes and 2 no.

DR. LASKEY: If each panel member could take 60 seconds to defend their position.

DR. WITTES: A short essay, right?

DR. LASKEY: Well, short.

DR. WITTES: To me, the data showed convincingly a sizable benefit, mortality at one year, but the device is risky, and so I believe the patients and their families should be informed of the likely risks and the time course of those risks.

DR. DOMANSKI: I think they demonstrated

safety and efficacy per the statutes.

DR. KONSTAM: I think that survival was extended. I didn't hear any disagreement about that. I think there were sizable numbers of patients who it appears from the data set were doing fairly well with a very, very high percentage of mortality in the control group.

I am concerned about the adverse events that were seen. I am concerned about the durability of the device and the fact that there was such low survival at two years, but that was not enough to negate the basic underlying finding of efficacy in terms of survival.

DR. COMEROTA: We have a treatment that doubled survival in one year with no device failure. There is an accompanying body of data that shows substantial improvement in the functional status of the patients albeit it that has come under some criticism.

There was a parallel increase in quality of life.

DR. NISSEN: I think this is a very promising therapy for heart failure, but this device is not ready, and I find it hard to accept a device that during an average duration of survival

of 400 days had a 30 percent internal failure rate.

The reason I am so concerned about that is that we all know the impact of approving a device, is there is a trickle-down in the device to patients very quickly beyond the group of patients studied in a trial like this, and labeling does not protect patients from that.

That trickle-down would be less concerning to me if the device were reliable, but the problem is it is not, and so if you put this device in patients that have a 92 percent risk of dying in two years, it is not too bad a bargain. If you put this device in patients that are a little bit less sick, now what you have done is replaced good medical therapy with not such good surgical therapy.

So, I think getting the device reliability up to a higher level of reliability would be essential for this to be a meaningful advance in the clinical treatment of such patients.

I think that that can be done, and I think it will be done, and I am concerned that based upon the outcome in 67 patients with a very high device failure rate, I do think we have opened Pandora's Box, and I don't want to be the purveyor of doom

and gloom, but I think this will be a decision that many people in the medical community will come to regret.

DR. AZIZ: I think that device therapy as an alternative to transplantation is going to be here to stay. I echo some of the comments of my colleague that I think the device should be carefully monitored. I think it does have a fairly high incidence of malfunction or dysfunction.

I think at one year, clearly, it works well, but I think it will be very important in the postmarket surveillance to watch that carefully, that this really does not get out of hand.

DR. PINA: I share Dr. Nissen's concerns about the device falling into the hands of people who are ill equipped to use them, and who are not going to apply proper medical therapy to the advanced heart failure patient. However, that does not negate the survival number at one year, which was their endpoint, and they have met it, and therefore, I don't think that we can sit here and say no, do not approve it.

I do share some of the very concerns that Dr. Nissen has expressed, and I think we have couched this with a lot of conditions, and I am

hoping and really hoping beyond hope that the company will take this to heart and apply it only to those populations that need it, and put it in centers where people do know what they are doing, and try to control the trickling-down effect which we have already seen with other devices.

DR. OSSORIO: While I was impressed by the survival numbers, I am still not convinced that there is real clinical significance, and until I see more and better data, and I feel very torn about this and knowing that other people had already voted in a way that it would be approved with these conditions, it left me open to express my feeling that this really should have come to us a little bit later where there were more data for us to evaluate.

I think the number of conditions that were put on this actually was part of what convinced me that a lot of the other panel members feel strong discomfort about what was before us today. I think we should be voting to approve or not based on what we have seen before us, what we could evaluate.

We don't have I think adequate Quality of Life measures to evaluate. We don't have adequate description of what kind of training and labeling

there is going to be to evaluate. So, I voted no.

The other thing is that part of our assessment of safety has to be an assessment of whether the harms have been reduced as well as they could be, and I think that is where the adverse events data, and so forth, call into some serious questions with respect to the standards that we are supposed to be applying.

DR. DeWEESE: I am convinced by the survival information. I feel confident that the final group deciding these things will be sure that these are performed in transplant centers by capable people, and that it will be limited to people who cannot be transplanted.

DR. KLOCKE: My question is that the long-term beneficial effect of this device will depend crucially on the degree to which the current incidence of adverse events can be reduced. If it can't be reduced, the data we have will still stand, but my hunch is that after a period, that clinical acceptance will be in fact limited, and if the genie does get out of the bottle, we make go through a period, as we did with transplant, where we have a disappointing experience because the genie out of the bottle.

That will be unfortunate, but it will be transitory, but I believe that the key event for this long term is the degree to which we can improve further on the incidence of adverse events.

DR. OSSORIO: Can I say one more thing?

DR. LASKEY: Yes.

DR. OSSORIO: I also just wanted to say that part of the reason I am very torn about this is because in other contexts, in the cancer context, I have dealt a lot with patients who are really at the end of life, and I think it is very important for us not to be making value judgments as to whether or not one year is long enough.

If I really believed the data, or it's not that I don't believe the data, if I really had enough data to convince me, then, I would have voted for approvability, but giving patients additional choices, especially additional choices with lots of uncertainty, is also a burden to them.

It is not merely a benefit to have a lot of choices. It also adds then responsibilities to their lives, decisions they have to make, which we have data on the fact that these decisions are very stressful for people to make.

So, I don't want it to seem as though I am

insensitive to the needs and desires of patients, but I think it is not always doing anybody a favor to give them an option where we can't tell them enough about it, and we can't tell them the kinds of things they would like to know to help them make their decision.

DR. LASKEY: Mr. Dacey or Mr. Morton, any final thoughts?

If not, I would just like to reopen for one last time the public forum. Are there any public comments?

[No response.]

DR. LASKEY: If not, then, I thank all participants, in particular the presenters, for their participation and for their endurance.

I close this portion of our panel meeting.

[Whereupon, at 5:50 p.m., the proceedings were recessed, to be resumed on March 5, 2002, at 8:00 a.m.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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